UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

FROM: Kathryn Boyle, CoChair IIFG

and

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TO: Robert Forrest, Chief
Minor Use, Inerts, and Emergency Response Branch

SUBJECT: IIFG Decision Document on Tolerance Reassessment for Methoprene

The Inert Ingredient Focus Group reassessment is based on various conclusions of the FAO/WHO Joint Expert Committee on Food Additives, information previously used by OPP as part of the reregistration process, and other information available on government websites.

In total 37 tolerances are reassessed.

INERT INGREDIENT FOCUS GROUP

DECISION DOCUMENT for

Methoprene

Petition No.: no

Tolerance Reassessments?: yes

Chemical Category/Group: fatty acid ester derivative

Methoprene is a racemate, a mixture of R and S stereoisomers. S-methoprene is the form that functions as a pesticide active ingredient (insect growth regulator). Methoprene and S-methoprene are equivalent from the perspective of mammalian toxicity.

Chemical Name: Methoprene: isopropyl (2E, 4E) -11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate, S-methoprene: isopropyl (2E, 4E, 7S) -11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate

CAS Reg. No.: 40596-69-8 (methoprene), 65733-16-6 (S-methoprene)

Mode of Pesticidal Action: Methoprene is regulated as a biochemical pesticide. It is an insect growth regulator that mimics juvenile hormones. When applied to larval stages, it effectively prevents metamorphosis to viable adults.

Methoprene was first registered in 1975. The Reregistration Eligibility Decision Document (RED) was issued in 1991. This document is located on the EPA website: http://www.epa.gov/oppsrrd1/REDs/old_reds/methoprene.pdf. Some of the pests controlled by methoprene include flies, mosquitos, and ants. The following describes the various ways that methoprene is used.

Table 1: Use Pattern (pesticidal - active ingredient)

Chemical Name/ PC Code	40 CFR 180.	Use Pattern (Pesticidal)
S-methoprene 105402 Methoprene 105401	359	Numerical Tolerances ranging from 0.1 to 25 ppm Use as an animal feed-through; grain products (post-harvest), mushrooms, peanuts
	1033	Tolerance Exemption on all raw agricultural commodities

There are also uses in food processing plants and eating establishments. Additionally, there are the following non-food use sites: tobacco, ornamentals, turf (including golf course uses), pet products, uses in and around the home, ditches and impoundments, swamps and marshes, and boxcars. It can be applied by aerial application. There are 71 registered products containing S-methoprene or methoprene.

The specific numerical tolerances are:

Table 2: Comparison of EPA Tolerances and CODEX MRLs

Commodity	Tolerance (ppm)	MRL (mg/kg)
barley	5.0	---
buckwheat	5.0	---
cattle, fat	1.0	---
cattle, meat	0.1	---
cattle, meat byproducts	0.1	---
cereal grain milled fractions (except flour and rice hulls)	10	---
corn (except popcorn and sweetcorn)	5.0	---
egg	0.1	0.05
goat, fat	1.0	---
goat, meat	0.1	---
goat, meat byproducts	0.1	---
hog, fat	1.0	---
hog, meat	0.1	---

hog, meat byproducts	0.1	---
horse, fat	1.0	---
horse, meat	0.1	---
horse, meat byproducts	0.1	---
milk	0.1	---
millet	5.0	---
mushroom	1.0	0.2
oat	5.0	---
peanut	2.0	2
poultry, fat	1.0	---
poultry, meat	0.1	---
poultry, meat byproducts	0.1	---
rice	5.0	---
rice, hulls	25	---
rye	5.0	---
sheep, fat	1.0	---
sheep, meat	.01	---
sheep, meat byproducts	.01	---
sorghum (milo)	5.0	---
wheat	5.0	---
wheat bran, unprocessed	---	10
wheat flour	---	2
wheat whole meal	---	5
cereal grains (post-harvest treatment)	---	5
maize, oil (edible)	---	0.2
meat (mammal)	---	0.2

Safety Assessment of Methoprene

1. Physical/Chemical Properties:

The physical and chemical properties of methoprene are described in the 1991 RED.

2. Information Sources:

The following information was used in performing this assessment. The available information consisted of information retrieved from various websites, such as:

- EPA (www.epa.gov),
- TOXNET (www.toxnet.nlm.nih.gov.),
- WHO (www.inchem.org/documents/jmpr/jmpmono/v84pr61.htm) and (www.inchem.org/documents/jmpr/jmpmono/v84pr31.htm)

Also, an article from open literature: Breaud T.P., *et. al.*(1977). Effects of the Insect Growth Regulator Methoprene on Natural Populations of Aquatic Organisms in Louisiana Intermediate Marsh Habitats. Mosquito News. 37(4):704-712.

3. FAO/WHO JMPR (Joint Meeting on Pesticide Residues)

The JMPR evaluation occurred in 1984. Some of the data evaluated by EPA in the 1991 RED was not available for the 1984 evaluation, most notably, the chronic/carcinogenic mouse study used to establish the RfD.

Currently, the acceptable daily intake is 0 to 0.09 mg/kg/day for the R,S racemate and 0 to 0.05 mg/kg/day for S-methoprene. JMPR documentation noted that an acute RfD was unnecessary.

4. Toxicological Profile Table

The information in this table is based to a large extent on the summaries of the data reviews extracted from the 1991 RED. However, as appropriate and necessary, the studies were rereviewed during this evaluation.

Table 3: Toxicological Profile

Study	Toxicity
Acute oral toxicity (rat)	LD_{50} is greater than 10,000 mg/kg (toxicity category IV)
Acute oral toxicity (dog)	LD_{50} is between 5000 and 10,000 mg/kg (toxicity category IV)
Acute dermal toxicity (rabbit)	LD_{50} is greater than 2000 mg/kg (toxicity category III)
Acute inhalation toxicity (rat)	LC_{50} is greater than 20 mg/L (toxicity category IV)
Primary eye irritation	Not an eye irritant (toxicity category IV)
Primary skin irritation	Not a skin irritant (toxicity category IV)
Dermal sensitization	Not a sensitizer
90-day oral toxicity(rat)	Doses: 0, 250, 500, 1000, or 5000 ppm (0, 12.5, 25, 50, or 250 mg/kg/day) NOAEL determined to be 500 ppm based on the LOAEL (reversible renal tubular degeneration) at 1000 ppm
90-day oral toxicity (dog)	Doses: 0, 250, 500, or 5000 ppm (0, 6.25, 12.5, or 125 mg/kg/day) NOAEL determined to be 500 ppm based on the LOAEL (increased liver weights) at 5000 ppm
30-day dermal toxicity (rabbit)	Doses: 0, 100, 300, 900, or 2700 mg/kg/day NOAEL determined to be 100 mg/kg/day based on the LOAEL(decreased body weight gain) at 300 mg/kg/day

21-day inhalation toxicity (rat)	Doses: 0, 2, or 20 mg/L. NOAEL was determined to be 20 mg/L (3408 mg/kg/day) (HDT)
Chronic (2-year) toxicity (rat)	Doses: 0, 250, 1000, or 5000 ppm (0, 12.5, 25, 50, or 250 mg/kg/day). NOAEL = 5000 ppm (HDT)
Chronic (18-month) toxicity (mice)	Doses: 0, 250, 1000, or 2500 ppm (0, 37.5, 150, or 375 mg/kg/day) NOAEL determined to be 250 ppm based on the LOAEL (liver lesions) at 2500 ppm
Carcinogenicity - mice & rats	No evidence of carcinogenicity
Developmental toxicity (rabbit)	Doses: 0, 50, 200 or 2000 mg/kg/day. Maternal/Developmental NOAEL = 2000 mg/kg/day (HDT).
Developmental toxicity (mice)	Doses: 0, 50, 200, or 600 mg/kg/day. Maternal/Developmental NOAEL = 600 mg/kg/day (HDT)
Reproductive toxicity (rat)	Weanlings dosed: 0, 500, or 2500 ppm. Parental NOAEL = 500 ppm (50 mg/kg/day) based on decreased weight gain at 2500 ppm (250 mg/kg/day) (LOAEL). Reproductive toxicity NOAEL = 50 mg/kg/day based on decreased pup weights and increased number of still births at 250 mg/kg/day (LOAEL).
Mutagenicity	Not mutagenic in Ames assay w/wo activation and dominant lethal study in rats.
Metabolism	Studies in four species indicate rapid and extensive biodegradation of methoprene and its metabolites in mammalian species. Methoprene metabolites are incorporated into natural body constituents.

5. Doses and Endpoints for Use in Risk Assessment

Acute Dietary

No acute (1 day or single exposure) endpoint was identified.

Chronic RfD

The chronic dietary endpoint is the systemic NOAEL of 37.5 mg/kg/day based on a dose-related increase in the incidence and the severity of liver lesions characterized by pigment deposition in the cytoplasm of liver parenchymal cells observed at 150 mg/kg/day (LOAEL) in an 18-month chronic toxicity/carcinogenicity feeding study in mice. An uncertainty factor (UF) of 100 (10X for interspecies differences to account for extrapolation from animal data to humans and 10X for intraspecies differences to account for differences in sensitivity in the human population) is applied to the NOAEL to achieve a Reference Dose (RfD) of 0.4 mg/kg/day.

Short-Term

No short-term (1 to 7 days) endpoint was identified.

Intermediate-Term

The intermediate-term **incidental oral** endpoint is a NOAEL of 50 mg/kg/day based on slight decreases (not statistically significant) in mean pup weight and increases in still births observed at the highest dose tested (LOAEL = 250 mg/kg/day) in a rat 3-generation reproductive toxicity feeding study. Weanling rats were exposed in the feed at 0, 500, or 2500 ppm (0, 50 or 250 mg/kg/day) until at least 100 days of age prior to mating. Parental NOAEL = 50 mg/kg/day based on decreased weight gain at 250 mg/kg/day (LOAEL). Reproductive toxicity NOAEL = 50 mg/kg/day based on decreased pup weights and increased number of still births at 250 mg/kg/day (LOAEL). This study is appropriate for both the duration (1-6 months) and population (toddlers/children) of concern. A Margin of Exposure (MOE) of 100 (based on the UF of 100) is considered adequate for risk assessment purposes for intermediate-term exposure oral incidental exposure.

Although 90-day subchronic toxicity studies are available in both rats and dogs, they are inappropriate for endpoint selection. In the dog study, elevated alkaline phosphatase levels in males and increased liver weights in both sexes were observed at the highest dose tested, 5000 ppm (250 mg/kg/day). In rats, increased liver weights in both sexes and increased kidney weights in males were observed at the highest dose tested, also 5000 ppm (125 mg/kg/day). A rare focus of renal tubular regeneration in 7 male rats at 5000 ppm and 3 male rats at 1000 ppm (50 mg/kg/d) was observed; however, the study authors considered these effects to be reversible and not to have an affect on kidney function. The study authors suggest that the 5000 ppm dose level, for both rats and dogs, is excessive and produced stressful metabolic changes such as the elevation of the blood serum level of alkaline phosphatase and the increased organ weights.

Cellular metabolism and cell membrane permeability can be affected by excessive chemical exposure, leading to increased blood enzyme levels caused by cell loss of enzyme. Both the elevated enzyme levels and the increased organ weights would be expected to return to normal ranges when exposure to the compound ends (i.e. reversible effect).

Route specific **dermal and inhalation** studies are available. The dermal endpoint is a NOAEL of 100 mg/kg/day based on decreased body weight gain seen at 300 mg/kg/day (LOAEL) in a 30-day dermal toxicity study in rabbits. It should be noted that this is considered a highly conservative dermal endpoint. The log K_{ow} of 5.5 suggests very low dermal absorption. The skin of the rabbits was neither abraded nor occluded. There was also no indication that the animals were collared to prevent licking (i.e., potential for oral dosing). In a 21-day inhalation study in rats, no effects were seen at the highest dose tested, 20 mg/L (3408 mg/kg/day) (NOAEL). An MOE of 100 is considered adequate for intermediate-term dermal and inhalation exposure.

Aggregate Assessment

Potential risks from exposures via the oral, dermal and inhalation routes cannot be aggregated since the toxic effects observed in the studies used for endpoint selection are dissimilar.

6. Human Health Hazard Characterization:

In general, methoprene is of low toxicity. Submitted data and literature studies indicate that methoprene is not acutely toxic. It is also neither irritating to skin or eyes, nor is it a dermal sensitizer (toxicity category IV). These findings are consistent with those of the World Health Organization (WHO). No acute dietary or short-term (residential) endpoints were selected. Developmental toxicity was not observed in studies with rabbits and mice. Though some reproductive toxicity (i.e., non-statistically significant decreased pup weight and increased incidence of stillbirths) was observed at the highest dose tested in the 3-generation study in rats, parental toxicity was also observed at this dose. Methoprene is not carcinogenic in studies in rats and mice. Methoprene was not mutagenic in the Ames assay with and without activation or in the dominant lethal assay. Following long-term or chronic exposure, methoprene caused liver lesions at 150 mg/kg/day in mice (NOAEL 37.5 mg/kg/day). No adverse effects were seen in rats in a 2-year study. Though decreased body weight gain was observed in a 30-day dermal toxicity study in rabbits at 300 mg/kg/day (NOAEL = 100 mg/kg/day), dermal absorption and toxicity are expected to be low. No effects were observed in a 21-day inhalation study in rats at the highest dose tested, 3408 mg/kg/day. Metabolism studies in rats, mice, guinea pigs, and cows indicate rapid biodegradation of methoprene and its metabolites in mammals and that its metabolites are incorporated into natural body constituents (primarily fatty acids).

The toxicity data base is adequate and no additional data are needed to assess the safety of

methoprene.

7. Type of Risk Assessment/Risk Characterization:

Methoprene is a low toxicity chemical. Given the available data, screening level quantitative risk assessments were conducted for intermediate-term scenarios and included all pathways of human exposure (food, drinking water, and residential). For chronic exposure scenarios, only the dietary pathways (food and drinking water) were considered to be appropriate.

8. Sensitivity of Infants and Children:

The FQPA Safety Factor is reduced to 1x. No effects were seen in developmental toxicity studies in mice and rabbits. In the 3-generation reproductive toxicity study in rats, slight decreases (not statistically significant) in pup weights and an increased incidence of still births were seen at the highest dose tested. However, decreased weight gain in the parents was also seen at the same dose. None of these effects were seen at lower doses or in controls. There is a low degree of concern because: 1) a clear NOAEL has been established for the pup effects; 2) studies evaluating *in utero* exposure did not show fetotoxicity; 3) post-natal pup effects have a well characterized dose-response curve; and 4) although numerically close, the NOAEL of 37.5 mg/kg/day for long-term exposure is below the reproductive NOAEL of 50 mg/kg/day and is therefore protective of these effects. In addition, neurotoxicity or neuropathology were ***not*** observed in any available study. Though not an expected route of exposure, subcutaneously exposed rats and mice showed no estrogenic, androgenic, anabolic or glucocortical activity in studies designed to measure endocrine activity in mammals. ***The weight-of-evidence supports reducing the FQPA factor to 1x.***

9. Dietary Risk Assessment

The Agency has developed a dietary exposure assessment for use as a screening tool for chemicals that have a wide-ranging dietary component to their exposure profile. Such wide-ranging dietary exposure usually occurs as a result of an exemption from the requirement of a tolerance.

The screening level dietary exposure assessment is highly conservative. It uses the USDA's Continuing Surveys of Food Intake by Individuals (1989-1992 data) as the basis for food consumption and assumes that all food forms contain residues of the chemical in question. The residue levels are based on tolerance levels for widely used crop protection chemicals. The screening level dietary exposure assessment was based on an application rate of 5 pounds per acre.

However, application rates for methoprene-containing formulations do not exceed 1 pound per acre. It is reasonable, therefore, to assume that dietary exposure to methoprene will be conservatively estimated by using one fifth of the exposure estimates listed in the screening-level

dietary assessment. The dietary exposure estimates from the generic screening analysis and for methoprene are shown in Table 4 for the representative population subgroups captured in the survey data from 1989 to 1992. Note that there have been no adverse effects attributable to a single exposure to methoprene. As such, an acute dietary assessment is not required for methoprene: Table 4 provides only chronic dietary exposure estimates.

Table 4: Generic Screening and Methoprene Chronic Dietary Exposure Estimates

Population subgroup	Dietary Exposure, mg/kg/day	
	Generic Screening Estimate	Methoprene Estimate
U.S. General Population	0.12	0.024
All Infants (< 1 year old)	0.28	0.056
Children (1-6 years old)	0.32	0.064
Children (7-12 years old)	0.16	0.032
Females (13-50 years old)	0.09	0.018
Males (13-19 years old)	0.11	0.022
Males (20+ years old)	0.09	0.018
Seniors (55+ years old)	0.09	0.018

10. Residential Risk Assessment

A quantitative intermediate-term exposure and risk analysis was performed for methoprene. There are no acute toxicological concerns for methoprene, thus an acute risk assessment is not appropriate. A chronic risk assessment is not appropriate as the methoprene use patterns do not indicate any chronic exposure scenarios. However, the use patterns suggest that there may be intermediate-term exposures. Using the doses and endpoints discussed in section 5 the following scenarios were assessed:

- Adult exposures from application of an aerosol spray can;
- Adult exposures from mixing/loading/applying liquids with a low pressure handwand;
- Toddler dermal exposures from petting animals that are wearing a treated pet collar; and,
- Toddler oral exposures from hand-to-mouth activities resulting from petting animals that are wearing treated pet collars.

In all four of the exposure scenarios assessed, the MOEs were well over 100 and thus did not present a risk of concern for methoprene, when considering only the residential use patterns of

methoprene. The details of the residential risk assessment are available in a supplemental memo titled "Methoprene Exposure and Risk Analysis. " Table 5 is a summary of the MOEs for each of the scenarios of concern:

Table 5: Summary of Methoprene Intermediate-Term MOEs

Scenario	Exposed Population	Dermal MOE	Inhalation MOE	Incidental Oral MOE
Applicator - aerosol can	Adults	2,500	12,000,000	N/A
Mixer/loader/applicator – low pressure handwand	Adults	29,000	3,400,000,000	N/A
Dermal exposure from petting animals with treated collars	Toddlers	4,000,000	N/A	N/A
Incidental oral exposure from hand-to-mouth activities after petting animals with treated collars	Toddlers	N/A	N/A	9,300

All MOEs are greater than 100 considering only the residential uses of methoprene.

12. Environmental Fate and Water Quality Assessment:

Environmental Fate Summary

Methoprene's principle route of degradation and/or transformation under environmental conditions is likely to be microbial mediated metabolism (aerobic and anaerobic). However, in surface water with significant Secchi Indexes (transmission of light with depth or an indication of water clarity), photodegradation will be the dominant degradation pathway. Studies have indicated that rates of degradation are affected by temperature, i.e., degradation is more rapid at higher temperatures. Soil metabolism half-lives of 10 and 14 days in distinctly different soils have been reported with more than 50 percent of the radiolabeled mass being associated with CO_2. Remaining degradates were the hydroxy ester and its corresponding acids. Half-lives in poorly characterized pond water (limited water quality data reported) exposed to sunlight were more rapid than the reported soil half-lives: more than 80 percent of methoprene degraded within 13 days. Biologically mediated degradation contributed to the more rapid transformation of methoprene in the pond water based on reported data from a paired degradation study using both sterile and non-sterile pond water. These results suggest that although photodegradation plays a significant role is transformation in the laboratory, biodegradation in natural systems would likely remain the principle transformation process due to limited light penetration in many surface water systems. One major degradate was identified, methoxycitronellic acid. Dissipation, $DT_{90,}$ rates (combination of degradation, transformation and transport out of the system) of approximately 3

days following application of methoprene to aquatic systems were reported. Degradation occurs at about the same rate in freshwater and estuarine/marine systems.

Methoprene was immobile in four soil leaching columns with no reported residues below the 3 cm level. Degradation products were not monitored in the study. Sorption onto organic matter in soils and sediments is expected to be strong based on the estimated K_{oc} of 23,000 determined using the measured log K_{ow} of 5.5. Volatilization from dry surfaces such as soil is not expected to be significant based on a vapor pressure of 2.36×10^{-5} mm Hg. Partitioning from water into the atmosphere would be expected based on the Henry's Law constant of 6.9×10^{-6} atm-m^3 $mole^{-1}$ except that the relatively high water solubility (1.4 mg/L) and its tendency to sorb onto organic material and sediments will temper this process. Hydrolysis is not expected to be a significant degradation pathway at relevant environmental pH (pH 6-8).

The high bioconcentration factor (BCF) of 3400 estimate based on the log K_{ow} suggest a potential for bioconcentration in aquatic organisms. However, in a laboratory study on bluegill sunfish a BCF of 457 was determined. Concentrations in the test vessel were not maintained throughout the study. Concentrations in the fish tissue followed the declining trend in water concentrations towards the end of the study. An accumulation study is crayfish indicated a lower tendency for bioaccumulation than in fish. Maximum BCF observed was 75.

Water Quality Assessment Summary

Based on the available fate data, methoprene will likely reach surface water following runoff producing rainfall for several weeks following applications to terrestrial environments. Based on the water solubility and the sorption coefficient (K_{ow}), methoprene will be associated with both the dissolved and organic matter/soil particle sorbed fraction. Therefore, environmental exposures in surface water following application is likely. Based on the available fate data and Tier 1 environmental modeling using GENEEC (Generic Estimated Environmental Concentration) and FIRST (FQPA Index Reservoir Screening Tool), a one pound application applied 1 time per year results in a peak estimated environmental concentrations at the edge of the field in the low part per billion (<10 ppb) and below a part per billion for an annual average estimate. No surface water monitoring data were available in the open literature, the USGS National Water Quality Assessment Program, or the Office of Water's databases. There are no primary or secondary drinking water standards nor ambient water quality criteria for methoprene.

Methoprene is applied directly to non-potable and potable water, stagnant, saline, brackish and polluted waters. Exposure to methoprene and its degradation products from direct applications to water is limited to these aquatic environments, where mosquito breeding occurs. If methoprene were applied to water used as a source of drinking water, e.g. reservoirs and ox-bow lakes, dilution and residence time would reduce exposures to methoprene at the drinking water intake. Methoprene degrades relatively rapidly in natural water through photodegradation and metabolism. Modeled concentrations indicate exposures below 10 ppb and there may be little effect of repeat applications on peak and longer-term concentrations from terrestrial uses when methoprene treatments recur at intervals greater than 12 days. In estuarine environments where

tidal flushing occurs repeat applications are not expected to result in accumulation of methoprene.

Leaching to ground water is not expected to be a significant concern for methoprene. The high affinity for organic matter and soils/sediments coupled with the relatively rapid degradation in both aerobic and anaerobic environments, suggest limited potential to move to ground water except under conditions of preferential flow. Soil column leaching studies indicate that methoprene will remain in the top few inches of soil when applied to terrestrial environments. An aerobic soil metabolism study conducted on a sandy soil where the half-life was similar to a soil less vulnerable to leaching provides additional evidence that leaching will likely be insignificant. No environmental monitoring data for methoprene in ground water could be found.

13. Aggregate Risk Assessment/Summary of Risk

Chronic

Using the chronic RfD of 0.4 mg/kg/day, the chronic dietary risk considering exposure to food only is:

Table 6: Methoprene Chronic % RfD

Population subgroup	Methoprene Estimate of Dietary Exposure (mg/kg/day)	% RfD
U.S. General Population	0.024	6
All Infants (< 1 year old)	0.056	14
Children (1-6 years old)	0.064	16
Children (7-12 years old)	0.032	8
Females (13-50 years old)	0.018	4.5
Males (13-19 years old)	0.022	5.5
Males (20+ years old)	0.018	4.5
Seniors (55+ years old)	0.018	4.5

Usually, the risk from consumption of drinking water would also be estimated. However, given the low percent of the RfD that is occupied (the highest being 16%) and that concentrations in drinking water were estimated at less than 10 ppb (less than 1% of the RfD for both children and adults), the Agency does not believe it necessary to calculate DWLOCs. There are no concerns for chronic dietary exposure.

Intermediate-Term

The previous MOEs for residential uses of methoprene were all greater than 100. As previously stated in section 5: Potential risks from exposures via the oral, dermal and inhalation routes cannot be aggregated since the toxic effects observed in the studies used for endpoint selection are dissimilar. Therefore, only the incidental oral exposure can be added to the chronic dietary risk.

Table 7: Methoprene Intermediate-Term Risk

Population subgroup	Methoprene Estimate of Dietary Exposure (mg/kg/day)	Incidental Dietary Exposure (mg/kg/day)	MOE
All Infants (< 1 year old)	0.056	0.0054	820
Children (1-6 years old)	0.064	0.0054	720

There are no concerns for any oral, dermal, or inhalation intermediate-term exposures to methoprene.

14. Ecotoxicity

The following information was extracted from the 1991 RED.

Species	**Effect**
Mallard duck	acute oral LD_{50} is greater than 2000 mg/kg 8-day LD_{50} is greater than 10,000 ppm NOEC (no-observed effect concentration) of 3 ppm based on reproductive impairment at 30 ppm
Quail	no effects on reproduction at 30 ppm
Bluegill sunfish	96-hour LC_{50} = 1.52 ppm methoprene is moderately toxic to warm water, freshwater fish
Rainbow trout	96-hour LC_{50} is greater than 50 ppm methoprene is slightly toxic to coldwater, freshwater fish
Daphnia magna	48-hour EC_{50} = 89 ppb 42-day Chronic NOAEC = 27 ppb, LOAEC = 51 ppb methoprene is very highly toxic to freshwater invertebrates

Estuarine and marine invertebrates	methoprene is slightly toxic to very highly toxic on an acute basis

The following ecotoxicity data has also been evaluated by the Agency:

Species	**Effect**
Grass shrimp	96-hour LC_{50} is equal to or greater than 10 ppm
Eastern oyster embryo larvae	48-hour EC_{50} = 247 ppb
Mud crabs	12 to 15 day exposure inhibited gametogenesis at 1.3 ppm
Grass shrimp	chronic: NOAEC = 387 ppb, LOAEC = 972 ppb
Fathead minnow	early life stage: NOEAC = 48 ppb, LOEAC = 84 ppb
Daphnia magna	chronic: NOAEC = 27 ppb, LOAEC = 51 ppb
Mysid shrimp	96-hour LC_{50} = 106 ppb
Mysid shrimp*	28 day chronic: reproduction NOAEC is equal to or greater than 50 ppb; Growth NOAEC = 14 ppb, LOAEC = 25 ppb

* This information has not yet been evaluated (MRID 44022101)

The aerial application of methoprene at 0.01 lbs per acre as a mosquito larvicide poses the greatest potential for exposure to terrestrial and aquatic non target organisms. At this application rate the maximum exposure in shallow water (6 inches deep) would be approximately 7 ppb (assumes all active ingredient is dissolved in the water column immediately upon application). Maximum exposure from liquid products would result in 2.4 ppm on short grass. Granular, bait or pellets applied at the same rate may result in an exposure of approximately 0.1 mg/ft^2. In light of these estimated exposure levels neither endangered nor non-endangered birds and mammals, are at acute or chronic risk. A report by the Scientific Peer Review Panel of the Minnesota Metropolitan Mosquito Control District (MMMCD) (MRID 44022102) of January 1996 corroborated this conclusion in a multi-year field study with red-winged blackbirds.

Characterizing the risk to aquatic organisms is more complex than for terrestrial vertebrates. The previously mentioned MMMCD report discussed effects of methoprene on the leopard frog. The leopard frog experienced no mortality at the highest dose tested (1.31 ppm) and no reproductive impairment at $\leq$ 240 ppb. At 720 ppb such adverse effects as reduced body weight, increased time to complete metamorphosis and delayed development of hind appendages were observed. Although neither fish nor frogs appear to be at direct acute or chronic risk there is uncertainty as to the potential indirect effects resulting from methoprene's impact on the invertebrate community serving as their prey. This uncertainty is based on three concerns: 1) the

assumption that acute mortality to mosquito larvae and other equally or more sensitive invertebrates will occur; 2) 5 ppb was both a daphnia chronic reproduction effective concentration and a 21 day LC50 (MMMCD report) and 3) methoprene concentrations in water - estimated maximum (7 ppb) and targeted field dosage rate (2ppb) – resulting from larvicide applications are close to these toxic endpoints. These three factors suggest the potential risk to predators (vertebrates and invertebrates) and prey. Furthermore, repeated use within a season or from year to year is expected to increase the risk to the invertebrate community (Breaud, T.P. et al. 1977) and subsequently to the aquatic vertebrate community if present.

15. Cumulative Exposure:

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide chemical's residues and "other substances that have a common mechanism of toxicity." EPA does not have, at this time, available data to determine whether methoprene has a common mechanism of toxicity with other substances or how to include these substances in a cumulative risk assessment.

16. Determination of Safety:

Based on its review and evaluation of the available information, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to residues of methoprene. Therefore, the numerical tolerances in 40 CFR 180.359 and the exemption from the requirement of a tolerance in 40 CFR 180.1033 are reassessed.

17. IIFG Recommendation/Deferral to BPPD Management

At this time 40 CFR 180.1033 specifies that methoprene is exempt from the requirement of a tolerance in or on all raw agricultural commodities when used to control mosquito larvae. There are also numerical tolerances for specific commodities in 40 CFR 180.359.

The methoprene risk assessment in this decision document used conservative assumptions that assumed the existence of a broad-based tolerance exemption. A broad-based tolerance exemption assumes that methoprene can be used on all crop commodities and that these crop commodities can be used as feed. The safety finding supports the tolerance exemption approach.

Therefore two issues remain, which need to be addressed by the Biopesticides and Pollution Prevention Division: First, the inconsistencies (tolerance versus tolerance exemption) need to be resolved. Second, consideration needs to be given to the fact that revocation of the numerical tolerances would mean lack of harmonization with the existing CODEX MRLs.

Attachment: